Telomerase

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Telomerase is an enzyme that adds specific DNA sequence repeats, ("TTAGGG" in all vertebrates) to the 3' ("three prime") end of DNA strands, in the telomere regions at the ends of chromosomes. The enzyme is a reverse transcriptase that carries its own RNA template; the RNA is used as a template for DNA synthesis.

It was discovered by Elizabeth Helen Blackburn.

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Human telomerase is composed of at least two subunits, Telomerase Reverse Transcriptase (hTERT, the 'h' is for human) and hTR (Telomerase RNA). These two subunits are coded for by two different genes in the genome. The coding region of the hTERT gene is 3396bp, which translates to a protein of 1131 amino acids. The polypeptide folds with the hTR subuint, which is not translated and remains as RNA. hTR is 450bp long. hTERT has a 'mitten' structure that allows it to wrap around the chromosome to add basepairs. Check out this site for a cool 3D model of telomerase <[1] (http://www.mun.ca/biochem/courses/3107/images/telomerase_model.gif)>

hTERT is a reverse transcriptase, which is a class of enzymes that creates single stranded DNA using single stranded RNA as a template. These enzymes are utilized in processes such as Reverse Transcriptase PCR, which lets you create a DNA copy of a gene using its mRNA as a template, and the HIV virus uses a reverse transcriptase to make DNA copies of its RNA genome for insertion into human cell chromosomes. hTERT carries its own template around, hTR. Using this template, it can add a six nucleotide repeating sequence, 5'-TTAGGG (in humans and all vertebrates...the sequence differs in other organisms), to the 3' strand of chromosomes. This repeating TTAGGG sequence is called the telomere. The template region of hTR is 3'-CCCAAUCCC. This way, telomerase can bind the first three C's of the template to the last three G's on the chromosome, add a new TTAGGG sequence, let go, grab on to the new G's, and repeat the process.

The telomere is a structure composed of these TTAGGG repeating sequences and various proteins and acts to protect the terminal ends of chromosomes. This prevents chromosomal fraying and fusion between chromosomes. However, because of DNA replication mechanisms, the telomeres shrink a little bit every time a cell divides. Therefore, telomerase is necessary to maintain the chromosomes of 'immortal' cell lines, those that can divide forever. If telomerase is not present, a cell can divide only about 50-90 times before the telomeres are too short to offer the chromosomes protection. When the telomeres are this short, cell division stops, and the cell has reached the Hayflick Limit. This is the case with most human body tissues, and is one of the reasons why we cannot live forever.

Telomerase and Cancer

Sometimes, a cell does not stop dividing once it reaches the Hayflick Limit. This means the telomeres are lost, and the integrity of the chromosomes declines with every subsequent cell division. Exposed chromosome ends are

interpreted as a double stranded break (DSB) in the genome, which is normally fixed by sticking the ends back together. The cell does this, but sticks together the ends of different chromosomes! This temporaraly solves the problem of no telomeres, but during anaphase of cell division the fused chromosomes are randomly ripped appart causing many mutations. As this process continues, the cell becomes very unstable and reaches a critical point: it must either undergo programmed cell death (apoptosis), or because of one of the random mutations, telomerase has to be turned back on. (The genes for telomerase are present in every cell in the body, they are just silenced in most). If this occurs, telomerase become active, the telomeres are rebuilt and the cell becomes stable.

The cell that is severely mutated and has active telomerase could very well be a cancerous cell (providing it has the correct mutations). Cancer cells are considered 'immortal' because telomerase activity allows them to divide forever, which is why they can form a tumor. A good example of cancer cells' immortality is HeLa cells. HeLa cells were originally removed from the cervical cancer of Henrietta Lacks in 1951 and are still used in laboratories as a model cell line. They are indeed immortal - daily production of HeLa cells is estimated at several tons - all from the few cells taken from Ms. Lacks' tumor.

Cancer is a very difficult disease to fight because the immune system cannot recognize it, and cancer cells are immortal; they will always continue dividing. Because telomerase is necessary for the immortality of 80% of all cancer types, it is thought to be a potential drug target. If a drug can be used to turn off telomerase in cancer cells, the above process will repeat itself: telomeres will be lost as the cells continute to divide, mutations will occur and cell stability will decrease. However, the cells would only have one option when they arrive at the critical point, they must die, because the drug would block telomerase activity.

Role in human disease

In humans, the telomerase starts is codified in the gene called hTERT (Human Telomerase Reverse Transcriptase). Its gene is located near the end of the bottom of chromosome 5, and it is only expressed by haploid cells (like sperm or ova), or very young somatic cells in infancy, stem cells and finally in special bone marrow cells that pass through the thymus gland and become initiated as thymic initiated cells (T-cells). Its from these T-cells, that our bodies receive a distributed small amount of telomerase, that peaks at adolescence and then begins to diminish in time, until the thymus gland all but disappears, along with the production of T-cells and thereby telomerase to the rest of our cells, until we have practically no more telomerase enzyme at the age of 45 years old, since there is no more thymus gland either. Its important to note here that several tissues are constantly renewed by their specific stem cells, for example skin epithelium and olfatory neurons, as such they have certain levels of telomerase activity independent of T-cells influence.

Children born without the thymus gland (Progeriacs), without the production of this enzyme (Werner syndrome) or people with trauma or diseases of the thymus gland, (Myasthenia gravis) begin to age quickly, without a thymus and the production of telomerase via the thymus-initiated cells (T-cells) telomerase distribution system (the lymphatic system).

External links

- Telomerase enzyme and leukemia (http://www.thedoctorslounge.net/oncolounge/articles/telomleuk/index.htm)
- Telomerase.org - free research abstracts list in PDF format. (http://www.telomerase.org/)

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